RESPONSE

I. Restriction Requirement

The Examiner has taken the position that the pending claims are drawn to five inventions that are allegedly not linked so as to form a single general inventive concept under PCT Rule 13.1. The inventions are set forth as:

Group I: Claims 1, 2, 5, 8, 9, 10, 22 and 23, said to be drawn to a method of identifying modulators of AMPK-mediated activation of a nitric oxide synthase enzyme comprising the special technical feature of testing putative modulators for their ability to mediate the phosphorylation of Ser-1177 depending on calmodulin and calcium ion concentrations;

Group II: Claims 3, 4, 6, 7, 9, 11, 22 and 24, said to be drawn to a method of identifying modulators of AMPK-mediated inhibition of a nitric oxide synthase enzyme having the special technical feature of testing putative modulators for their ability to mediate the phosphorylation of Thr-495 in the presence of limiting calcium ions;

Group III: Claims 1, 5, 6, 7, 12 and 13, said to be drawn to a method of identifying modulators of AMPK-mediated activation of a nitric oxide synthase enzyme having the special technical feature of testing putative modulators for their ability to mediate the phosphorylation of Ser-1417;

Group IV: Claims 14, 15, 17 and 19-21, said to be drawn to an antibody having the special technical feature of phosphorylating eNOS at Ser-1177; and

Group V: Claims 14, 16, 18 and 19-21, said to be drawn to an antibody having the special technical feature of phosphorylating eNOS at Thr-495.

The class and subclass of the inventions are not set forth.

II. Phosphorylation *vs.* Antibody Binding

Applicants respectfully point out that Groups IV and V have been improperly characterized. The antibodies of the invention do not phosphorylate eNOS (Requirement at pages 2 and 4). Rather, the antibodies bind to eNOS which is phosphorylated at Ser-1177 or at Thr-495.

III. Unity of Invention

As indicated in the Requirement, the appropriate standard for assessing the claims of the present application is unity of invention under PCT Rules 13.1 and 13.2. Rule 13.1 requires that the claims be linked so as to form a single general inventive concept, and Rule 13.2 requires that there be a technical relationship between the claims involving one or more of the same or corresponding special technical features.

Importantly, all claims were held to have unity of invention during the PCT examination phase. Despite this, Applicants choose to focus on the inventions said to be in Groups IV and V.

The Requirement attempts to separate independent claim 14, drawn to an antibody directed against eNOS phosphorylated at Ser-1177 or Thr-495, into two different restriction groups. In fact, claim 14 defines a single general inventive concept, such that the antibodies of claim 14 have a technical relationship and the same or corresponding special technical features. Thus, original Groups IV and V have unity of invention.

Claim 22 is drawn to a method of detecting phosphorylation of eNOS, comprising reacting a biological sample containing eNOS with an antibody according to claim 14 (emphasis added). Dependent claim 23 specifies the detection of phosphorylation at Ser-1177 and claim 24 specifies the detection of phosphorylation at Thr-495. Claim 22 is placed in both Groups I and II; claim 23 is said to be in Group I alone and claim 24 is said to be in Group II alone.

In fact, claims 22-24 have unity of invention with claim 14. This is clearly indicated in the Requirement itself, which acknowledges that unity is proper for "a product and a process of use of said product" (Requirement at page 3). As claim 14 defines an antibody product and claims 22-24 recite a process of use of the claimed product, claims 22-24 have unity of invention with claims 14-21.

IV. Election

As detailed above, at least Group IV, Group V and claims 22-24 form a unified invention under PCT Rule 13.1. Applicants elect the unified invention of Group IV, Group V and claims 22-24. The election is made without traverse as to restriction between the unified invention of Group IV, Group V and claims 22-24 and the inventions of Groups I, II and III. The election is made with traverse as to the initial restriction between Group IV, Group V and claims 22-24.

V. U.S. Restriction Practice

In addition to proper unity of invention under PCT Rules 13.1 and 13.2, the elected claims should be examined together under U.S. restriction practice.

Even if the application of U.S. restriction practice alone was appropriate, the Requirement has failed to establish that a serious burden will result should restriction not be made. The Requirement has also improperly ignored linking claims, the presence of which means that the inventions must be maintained together.

MPEP 806.05(c) states that a requirement for restriction must be supported by "both two-way distinctness and reasons for insisting on restriction". The instant Requirement has not provided sufficient reasons for insisting on restriction, and has not provided any evidence of two-way distinctness.

Even if the claims were drawn to "distinct inventions", MPEP 803 allows restriction only if a "serious burden" is imposed on the examiner should restriction not be made. "If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions."

MPEP 803. Search and examination of Group IV, Group V and claims 22-24 can be made without serious burden.

The Requirement has also ignored the linking claims. MPEP 809 mandates that, even with distinct inventions, "the linking claims must be examined with the invention elected, and should any linking claim be allowed, the restriction requirement must be withdrawn." Any claims to non-elected inventions, even if previously canceled, must then be reinstated in the case. MPEP 809. As the pending claims include proper linking claims, notably claims 14 and 22, all claims should be maintained in the case even if they are held to be drawn to distinct inventions.

Accordingly, Group IV, Group V and claims 22-24 define a unified invention, joined by proper linking claims, which can be examined without additional burden.

VI. Groups I, II and Ju *et al.*

Applicants reserve the right to pursue claims of inventions of Groups I, II and III in a divisional or other application claiming priority to the present case.

The Requirement takes the position that the methods of Groups I and II are anticipated by Ju *et al.* (Requirement at page 3). Ju *et al.* does not anticipate the methods of Groups I and II and does not destroy unity of invention.

Ju *et al.* reports that caveolin-1 interacts directly with eNOS via the oxygenase domain of eNOS, and that this interaction inhibits eNOS activation. This inhibition appears to result from interference with the interaction between and eNOS calmodulin. Fatty acylation of eNOS by myristate and palmitate also appears to be involved (Ju *et al.*, at page 18525, column 2). There is no teaching or suggestion that phosphorylation of eNOS might be in any way relevant to

activation or other modulation of the activity of eNOS. Thus, Ju *et al.* does not anticipate or render obvious the methods of Groups I and II and does not destroy unity of invention.

VII. Status of the Claims

Prior to the present amendment, claims 1-24 were in the case. Presently, claims 1-13 have been canceled without traverse. Claim 23 has been amended to correct a clerical oversight. No claims have been added. Claims 14-24 are therefore in the case. In accordance with 37 C.F.R. § 1.121, the pending claims are listed in the amendment section.

VIII. Support for the Claims

Support for the amended claim is to be found throughout the specification and claims of the original and parent applications. Claim 23 has been amended to correct a clerical oversight and to match claims 22 and 24, which provide the required support. It will therefore be understood that no new matter is encompassed by the present amendment.

IX. Sequence Listing

The Office has entered a sequence listing requirement in the above-referenced application. Applicants enclose a sequence listing diskette, paper copies of the sequence listing and the required statements. The present application is in compliance with the sequence listings requirements.

Amendments to the specification are also being made in regard to the sequence identifiers. The amendments are made solely to conform the specification to the enclosed sequence listing and are fully supported by the original application do not constitute new matter. The amendments to the specification comply with the revisions to 37 C.F.R. § 1.121, and separate exhibits are no longer necessary.

X. Conclusion

This is a complete response to the referenced Restriction Requirement and Sequence Listing Notice. The response is timely filed in light of the enclosed Request for Extension of Time and appropriate fee. No additional fees are required. However, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be deemed necessary, Applicants respectfully request a telephone call to the undersigned representative to discuss deduction from Applicants' representatives' Deposit Account No. 50-0786/4050.000900.

Should the Office have any questions, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,
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